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(54) Title: HIV AND CANCER TREATMENT

(57) Abstract

A method of treating HIV or other viral infections by administering a herbicide or fungicide or derivative thereof to an animal or human. The fungicides or herbicides can be used in conjunction with other treatments, e.g. with AZT or protease inhibitors for the treatment of HIV. For example, thiabendazole and chloropropham have been shown to quickly reduce the level of virus production from cell populations chronically infected with HIV-1 and the antiviral effect is maintained with continued compound exposure. This reduction of virus production occurs at concentrations which are non toxic to the host cell and which have no effect on the syntheses of cellular DNA, RNA and protein. Further, chronically infected cells treated for prolonged periods of time with thiabendazole and chloropropham were not super-infected with HIV. A method for inhibiting the growth of tumors and cancers in mammals comprising administering a herbicidal or fungicidal derivative is also disclosed herein. The fungicides or herbicides can be used in conjunction with other treatments, e.g. taxol for the treatment of breast cancer. Potentiators can also be included in the herbicidal or fungicidal composition. This method is particularly effective when the cancer or virus is an animal cell genetically modified by plant or fungus genetic material. A chemotherapeutic agent can also be administered first to significantly reduce the size of the cancer and then the treatment with the herbicide or fungicide is used. These methods are particularly effective when the cancer or virus is a mutated cell comprising plant or fungal genetic material.

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HIV AND CANCER TREATMENT

TECHNICAL FIELD

This invention is a method of inhibiting the growth of viruses, particularly HIV, cancers and tumors in human and warm blooded animals, involving the administration of herbicidal and fungicidal agents. Tumor size is decreased, the growth of the cancer is slowed, and the replication of viruses is inhibited. This treatment is particularly effective when the virus or cancer is the result of a mutated cell, i.e. an animal cell which has been mutated by incorporating therein genetic material from plants, fungi or molds.

BACKGROUND OF THE INVENTION

HIV and other viral infections are one leading cause of death. HIV is a disease in which a virus is replicated in the body which attacks the body's immune system. The HIV virus is not easily destroyed nor is there a good mechanism for keeping the host cells from replicating the virus. Herpes Simplex is another viral infection which is difficult, if not impossible, to cure. A method of treating these diseases and other viral infections is highly desirable.

Surprisingly, it has been found that fungicides, herbicides, mold inhibitors and their derivatives can inhibit the replication of viruses. The fungicides or herbicides can be used in conjunction with other treatments, e.g. with AZT, 3TC or protease inhibitors for the treatment of HIV. This HIV treatment is uniquely effective in the treatment of chronically infected cells and the cells do not appear to develop resistance to the treatment. For example, thiabendazole and chloropropham have been shown to quickly reduce the level of virus production from cell populations chronically infected with HIV-1 and the antiviral effect is maintained with continued compound exposure (up to one year). Furthermore this uniquely essentially complete suppression of virus production from chronically infected cells continues for up to 80 days after the drug is washed out and this "vaccine" effect is present in a dose response manner for both compounds. This latter effect is also unprecedented in the literature of HIV treatments. This reduction of virus production occurs at concentrations which are nontoxic to the host cell and which have no effect on the syntheses of cellular DNA, RNA and protein. Further, chronically infected cells treated for prolonged periods of time with thiabendazole and chloropropham were not super-infected with HIV. Furthermore and also unique to these compounds is the inability to induce a resistant strain after a year-long effort to do so. By

contrast, protease inhibitors induce resistant strains an this procedure in a matter of weeks and RT inhibitors all induce resistant strains in a month or two.

Cancers are a leading cause of death in animals and humans. The exact cause of cancer is not known, but links between certain activities such as smoking or exposure to carcinogens and the incidence of certain types of cancers and tumors has been shown by a number of researchers. However, what is known is that cancer cells are abnormal cells and can be dormant for a time and then rapidly grow. Many cancers cells are considered immortal because they do not die off like normal animal or human cells, but continue to replicate themselves.

Clearly, the development of materials that would target tumor cells due to some unique specificity for them would be a breakthrough. Alternatively, materials that were cytotoxic to tumor cells while exerting mild effects on normal cells would be desirable.

It is known plant and animal cells can be genetically altered by insertion of genetic material from a different cell type. These genetically altered cells have the DNA or portions of the genes or genetic material of one cell incorporated within the new cell. These new cells have the characteristics of both types of cells, but are no longer identified as wholly a plant or an animal cell. Such mutated or abnormal animal cells can be fast growing and do not respond as normal cells to the "aging" mechanisms.

The body has certain mechanisms for filtering out or eliminating molds, fungi and pollen materials. If they are ingested, the body's digestive system can eliminate or detoxify the materials in reasonable quantities. The nose, lungs and skin have active mechanisms for filtering foreign materials. However, there will always be plant, fungal and mold materials which penetrate the body's defense mechanisms and get into the blood stream, lymph system or penetrate the lung and skin membranes. These materials can penetrate animal cells and mutate them. The mutated cells can be made by the combination of plant cells with animal cells created by pollen combining with the animal cell. Pollen can be absorbed either through respiration wherein pollen is constantly bathing the lung tissues and other cells in the nose, mouth and throat with plant material. Other cells can be created by fungal materials or molds combining with the genetic material of the animal cells in the same way.

Abnormal or mutated cells which contain the genetic materials of both plant and animal or fungal and animal cells are environmentally altered cells. The body normally rejects these materials by creating antibodies, but when the cells have the characteristics of both the animal cell and the plant or fungal materials, including

molds, the antibodies may not function in the same way. This allows the cells to grow and since they are not normal, they can be called a "cancer" or tumor growth; including so-called "liquid tumors" such as leukemia.

Viruses also have the ability to invade cells and to replicate themselves within the cell matrix. These new cells are different from the two starting cells. Viruses themselves mutate and change based upon interactions with fungi, molds and plant material, particularly pollen. These viruses can also be destroyed or their replication inhibited by treatment with fungicides, mold inhibitors and herbicides. It is interesting that some of these compounds also act as anthelmintics.

It is interesting to note that 15% of cancers are caused by viruses. Also if one looks at the presence of fungi particularly that found in grasses, in a geography and the use of herbicides and fungicides to control the growth or proliferation of these materials, there is correlation to the incidence of cancer in the area. The more the fungal growth and vegetation is decreased by the broad use of herbicides and fungicides, the less cancer is present in that geography.

It is an object of this invention to provide a method of treating HIV wherein the virus production is inhibited. This method comprises the administration of a safe and effective amount of a herbicide or fungicide alone or in conjunction with other HIV drugs, e.g. AZT or 3TC.

It is a further object of this invention to provide an anti-viral therapy comprising administering a safe and effective amount of a viral growth inhibiting agent which has the ability to destroy viruses, particularly environmentally altered or mutated cells. The materials are herbicides which can destroy plant cells or fungicides which are effective against fungal materials, including molds. The agents may also be administered in conjunction with a potentiator, an anti inflammatory agent or vitamins, including antioxidant vitamins.

It is another object of this invention to provide an anti-cancer therapy comprising administering a safe and effective amount of a tumor reducing agent which has the ability to destroy cancer cells, particularly, environmentally altered cells. The materials are herbicides which can destroy plant cells or fungicides which are effective against fungal materials, including molds. The agents may also be administered with a chemotherapeutic agent either concurrently or in sequence and/or in conjunction with a potentiator.

These and other objects will become evident from the following detailed description of this inventions.

SUMMARY OF THE INVENTION

A method of treating HIV and other viral infections and cancers in mammals, and in particular, warm blooded animals and humans is claimed. The method comprises administering a safe and effective amount of a herbicide or a fungicide or derivative thereof which significantly reduces the mass of the tumor or cancer or inhibits the replication of viruses and cancer cells. The herbicidal agent and its derivatives are effective for treatment of cancers or viruses which are genetically altered animal cells made by combining a plant cell with an animal cell and the fungicidal agents and their derivatives are effective when the cancer or virus is an animal cell which contains genetic materials derived from a fungus or mold.

These compositions can be used to inhibit the growth of cancers and other tumors in humans or animals by administration of an effective amount either orally, rectally, topically or parenterally, intravenously or by injection into the tumor. Potentiators can also be used with this composition. The compositions can be used in conjunction with other therapies either sequentially or concurrently.

DETAILED DESCRIPTION OF THE INVENTION

A. DEFINITIONS:

As used herein, the term "comprising" means various components can be conjointly employed in the pharmaceutical composition of this invention. Accordingly, the terms "consisting essentially of" and "consisting of" are embodied in the term comprising.

As used herein, "mutated cell" or "environmentally altered cell" is an animal cell which has been genetically altered by combining genetic material, e.g. DNA or RNA fragments, from a plant or fungus cell with the genetic material of the animal cell to produce a new genetically modified cell which is neither a plant or fungus or animal cell but which is a viable parasite and remains in the host animal. Such a cell, when it grows and multiples, becomes a cancer cell in the host animal.

As used herein, a "pharmaceutically acceptable" component is one that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio.

As used herein, the term "safe and effective amount" refers to the quantity of a component which is sufficient to yield a desired therapeutic response without undue adverse side effects (such as toxicity, irritation, or allergic response) commensurate with a reasonable benefit/risk ratio when used in the manner of this

invention. The specific "safe and effective amount" will vary with such factors as the particular condition being treated, the physical condition of the patient, the type of mammal being treated, the duration of the treatment, the nature of concurrent therapy (if any), and the specific formulations employed and the structure of the compounds or its derivatives.

As used herein, a "pharmaceutical addition salts" is salt of the herbicidal or fungicidal agents and their derivatives with an organic or inorganic acid. These preferred acid addition salts are chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, malates, citrates, benzoates, salicylates, ascorbates, and the like.

As used herein, a "derivative" is a chemically modified derivative of the fungicide or herbicide compound which is more soluble or more easily metabolized but which has not had its efficacy as a herbicide or fungicide altered significantly. For example, addition of a hydroxyl group or other hydrophilic group will enhance the solubility and absorption by the body, and in most cases, not significantly affect the functionality of the compound. One skilled in the art can easily ascertain such compounds.

As used herein, a "pharmaceutical carrier" is a pharmaceutically acceptable solvent, suspending agent or vehicle, including liposomes, for delivering the anti-cancer agent to the animal or human. The carrier may be liquid or solid and is selected with the planned manner of administration in mind.

As used herein, "cancer" refers to all types of cancers or neoplasm or malignant tumors found in mammals, including tumors and leukemia.

As used herein "chemotherapeutic agents" includes DNA-interactive Agents, Antimetabolites, Tubulin-Interactive Agents, Hormonal agents and others, such as Asparaginase or hydroxyurea.

As used herein, "viruses" includes viruses which cause diseases (viral infection) in man and other warm blooded animals such as HIV virus, herpes, influenza and rhinoviruses.

As used herein "potentiators" are materials such as triprolidine and its cis-isomer and procodazole which are used in combination with the chemotherapeutic agents and herbicidal or fungicidal agents.

As used herein "significantly reduce" means to reduce the mass of the tumor by significant amount. This will usually be to less than 50% of its original mass, and preferably to reduce the mass to non-detectable amounts.

As used herein "fungicides" means a material which is effective in inhibiting the growth of fungi or killing a fungus. Mold inhibitors are included in the term "fungicide" since molds can be considered a fungus.

As used herein "herbicide" means a material which is effective in inhibiting the growth of plants, particularly those which kill the plant cells.

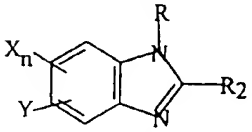
B. FUNGICIDES

Any number of fungicides and their derivatives and pharmaceutically acceptable salts can be used. The particular fungicide will be chosen for safety as well as its effectiveness in preventing the growth of the fungus. Broader spectrum fungicides are preferred. Some fungicides which have been shown to be effective are listed below.

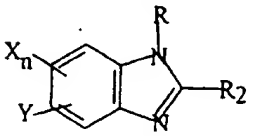
1. THE BENZIMIDAZOLES COMPOUNDS

The benzimidazole derivatives are known for their antifungal activities. Surprisingly it has been found that these compounds can also cause apoptosis in cancer cell lines. Apoptosis is specific cell death which differs from necrosis. Most cancer cells can live indefinitely; cancer cells are often referred to as immortalized cell lines. Therefore the ability to induce apoptosis is very important.

The compounds have the following structure:



wherein X is hydrogen, halogen, alkyl of less than 7 carbon atoms or alkoxy of less than 7 carbon atoms; n is a positive integer of less than 4; Y is hydrogen, chlorine, nitro, methyl or ethyl; and R is hydrogen, $CONHR_3$ and R_3 is alkyl of less than 7 carbons, preferably butyl or isobutyl or an alkyl group having from 1 to 8 carbons, and R_2 is $NHCOOR_1$ wherein R_1 is aliphatic hydrocarbon of less than 7 carbon atoms, and preferably and alkyl group of less than 7 carbon atoms. Preferably the compositions are:



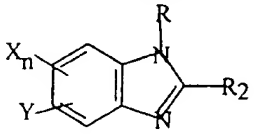
wherein R is hydrogen, $CONHR_3$ and R_3 is alkyl of less than 7 carbons, preferably butyl or isobutyl or an alkyl of 1 through 8 carbon atoms or the non-toxic, pharmaceutically acceptable acid addition salts with both organic and inorganic acids.

The most preferred compounds are methyl -(butylcarbamoyl)-2-benzimidazolecarbamate and 2-methoxycarbonylamino-benzimidazole and the compounds wherein Y is chloro and X is hydrogen. These compounds are prepared according to the method described in U.S. 3,738,995 issued to Adams et al. June 12, 1973.

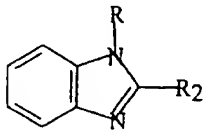
2. THIABENZIMIDAZOLE COMPOUNDS

Thiabendazole has been found to be particularly effective in the treatment of Chronic HIV where it has been shown to suppress viral production without the cells developing resistance to it.

The compounds have the following structure:



wherein X is hydrogen, halogen, alkyl of less than 7 carbon atoms or alkoxy of less than 7 carbon atoms; n is a positive integer of less than 4; Y is hydrogen, chlorine, nitro, methyl or ethyl; and R is hydrogen, $CONHR_3$ and R_3 is alkyl of less than 7 carbons, preferably butyl or isobutyl or an alkyl group having from 1 to 8 carbons, and R_2 is thiazolyl. Preferably the compositions are:

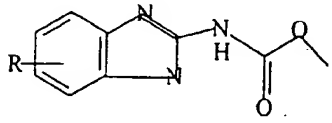


wherein R is hydrogen and R_2 is 4-thiazolyl or non-toxic, pharmaceutically acceptable acid addition salts with both organic and inorganic acids. The most preferred compounds are 2-(4-thiazolyl)benzimidazole. Thiabendazole is also an anthelmintic.

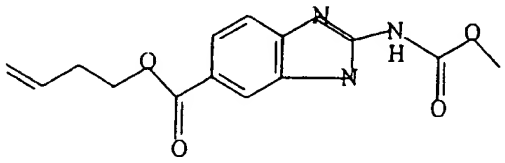
The thiazolyl derivatives are prepared according to the method described in Brown et al., J. Am. Chem. Soc., 83, 1764 (1961) and Grenda et al., J. Org. Chem., 30, 259 (1965).

3. Substituted benzimidazole derivatives.

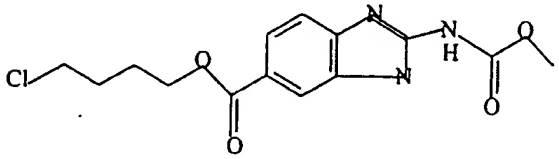
More soluble benzimidazole compounds are also useful in this invention. While these compounds are not known for herbicidal or fungicidal use, it is believed that they will be effective against HIV, cancer and other viral infections. These derivatives have the formula:



wherein R is selected from the group consisting of H, carboxyl ($-CO_2H$), hydroxyl, amino or esters ($-CO_2R'$) wherein R' is selected from the group consisting of alkoxy, haloalkyl, alkenyl, and cycloalkyl wherein the alkyl groups have from 1 - 8 carbons or $CH_3CH_2(OCH_2CH_2)_n$— or $CH_3CH_2CH_2(OCH_2CH_2CH_2)_n$— or $(CH_3)_2CH$- and



and$(OCH(CH_3)CH_2)_n$— wherein n is from 1-3. The preferred alkyl groups are straight chain. Preferably the halogen is substituted on the terminal carbon, and the halogen is chlorine. The preferred cycloalkyl groups are those having 3-6 carbon atoms. The cycloalkyl groups also include those which are substituted on an alkyl chain, 2-cyclopropylethyl, cyclopropylmethyl, 2-cyclopropyl propyl or 2-cyclopropylpropyl or cyclohexylmethyl. Preferred compounds are those having the formulas:



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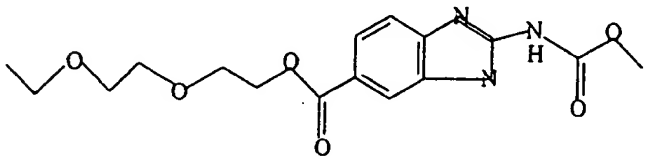

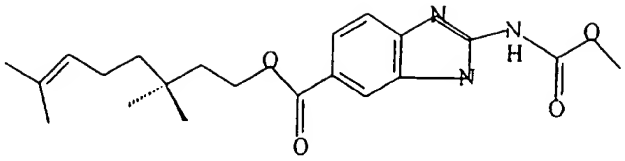

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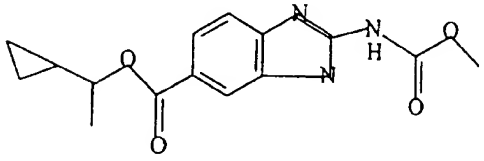

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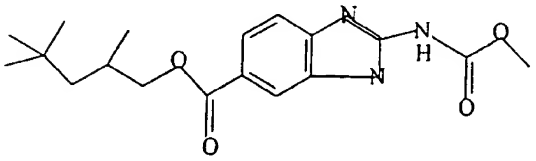
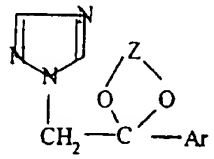


and their pharmaceutically acceptable salts.

4. 1H-1,2,4-triazole derivatives

1H-1,2,4-triazole derivatives are known for their antifungal activities. They are systemic materials used to prevent and eradicate fungi. The compounds have the following structure:



wherein Z is an alkylene selected from the group consisting of CH_2-CH_2-,-CH_2-CH_2-CH_2-, -$CH(CH_3)$-$CH(CH_3)$- and -CH_2-CH(alkyl) wherein said alkyl has from 1 to about 10 carbon atoms; and Ar is a member selected from the group consisting of phenyl, substituted phenyl, thienyl, halothienyl, naphthyl and fluorenyl, wherein "substituted phenyl" has the meaning of a phenyl radical having thereon from 1 to 3 substituents selected independently from the group consisting of halo, lower alkyl, lower polyalkoxy, cyano and nitro. The therapeutically active acid addition salts of the foregoing compound (I) are also embraced within the scope of this invention.

As used in the foregoing definition of Z, the term "alkyl" is meant to include straight and branch chained hydrocarbon radicals having from 1 to about 10 carbon atoms, such as, for example, methyl, ethyl, 1-methylethyl, propyl, 1,1-dimethylethyl, butyl, pentyl, hexyl, heptyl, octyl, decyl and the like; as used herein "lower alkyl" may be straight or branch chained saturated hydrocarbons having from 1 to 6 carbon atoms, such as, for example, methyl, ethyl, propyl, 1-methylethyl, butyl, 1,1-dimethylethyl, pentyl, hexyl and the like alkyls; and the term "halo" is generic to halogen atoms of atomic weight less than 127; i.e., fluoro, chloro, bromo and iodo.

Their pharmaceutically acceptable acid addition salts with both organic and inorganic acids can also be used herein.

Preferred derivatives include:

1-[2-(2,4-dichlorophenyl)-1,3-dioxolan-2-ylmethyl]-1H-1,2,4-triazole;

1-[2-(2,4-dichlorophenyl)-4-methyl-1,3-dioxolan-2-ylmethyl]-1H-1,2,4-triazole,

1-[2-(2,4-dichlorophenyl)-4-ethyl-1,3-dioxolan-2-ylmethyl]-1H-1,2,4-triazole,

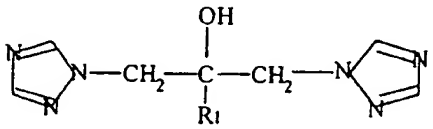
1-[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-ylmethyl]-1H-1,2,4-triazole,

1-[2-(2.4-dichlorophenyl)-4-pentyl-1,3-dioxolan-2-ylmethyl]-1H-1,2,4-triazole, and the therapeutically active acid addition salts thereof.

These compounds are prepared according to the method described in U.S. 4,079,062 issued to Van Reet. et al, Mar 14, 1978.

5. 1,3-Bis-triazolyl-2-propanol derivatives.

1,3-bis-triazolyl-2-propanol derivatives are known for their antifungal activities. They are systemic fungicides used to prevent and eradicate fungi. The compounds have the following structure:



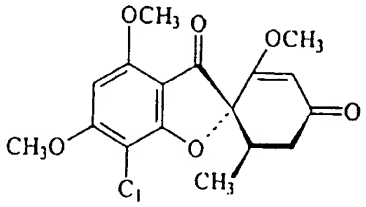
wherein R^1 is an optionally substituted alkyl, cycloalkyl (e.g. cyclopentyl or cyclohexyl), aryl or haloaryl (e.g. phenyl or 2,4-dichlorophenyl) or aralkyl (e.g., benzyl); and salts and metal complexes and ethers or esters thereof, and the non-toxic, pharmaceutically acceptable acid addition salts with both organic and inorganic acids. Specifically, such bis triazole derivatives as 2-(2,4-dichlorophenyl)-1,3-bis(1H-1,2,4-triazole-1-yl)propan-2-ol and its corresponding 2- and 4- chlorophenyl analogs and 2,4-diflourophenyl analogs are useful herein. Preferably the composition is 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-

yl)propan-2-ol and its pharmaceutically acceptable acid addition salts with both organic and inorganic acids.

These compounds are prepared according to the method described in U.S. 4,404,216 issued to Richardson, Sept. 13, 1983 and British Patent Application No. 2,078,719A published Jan. 13, 1982 and European patent application No. 44,605 published Jan. 27, 1982 (both assigned to Imperial Chemical Industries Ltd).

6. Griseofulvin

Griseofulvin has the following structure:



It is prepared according to the method described in U.S. 3,069,328 issued to Hockenhull (1962) and U.S. 3,069,328 issued to Dorey et al. (1962).

C. Herbicides

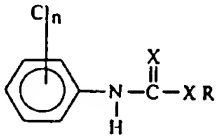
Any number of herbicides and their derivatives and the pharmaceutically acceptable salts can be used in the practice of this invention. Preferred herbicides are those described below.

1. N-chlorophenylcarbamates and N-chlorophenylthiocarbamates

N-chlorophenylcarbamates and N-chlorophenylthiocarbamates are known for their herbicidal activities. They are systemic herbicides used to prevent and eradicate certain plants or weeds. Systemic herbicides are differentiated from other herbicides by their ability to be absorbed by the plant and to move through the plant. This systemic ability is not a necessary requirement of the compounds of this invention.

Chloropropham, isopropyl N-(3-chlorophenyl)carbamate, has been shown to be particularly effective in the treatment of HIV.

The compounds have the following structure



wherein n is from 1 to 3, X is oxygen or sulfur and R is selected from the group consisting of hydrogen, lower alkyl and lower alkenyl, cyclohexyl, phenalkyl of up

to 8 carbon atoms and phenyl, and the pharmaceutically acceptable salts of these compounds.

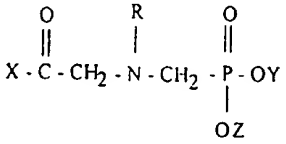
Preferred compounds are those in which R is alkyl with 1 to 4 carbons, preferably, isopropyl and X is oxygen, n is 1 and the chloro group is in the 3 position on the phenyl group. N-3-chlorophenylcarbamate is a most preferred compound.

These compounds are prepared according to the method described in U.S. 2,695,225 issued to Witman (1954) and U.S. 2,734,911 issued to Strain (1956).

2. N-Phosophonoglycines

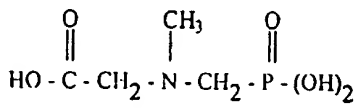
N-phosphonoglycine derivatives are known for their herbicidal activities. They are systemic herbicides used to prevent and eradicate certain plants or weeds.

The compounds have the following structure



wherein X is selected from the group consisting of hydroxy, thioyl, alkoxy or chloroxy up to 12 carbon atoms; lower alkenoxy, cyclohexyloxy, morpholino, pyrrlidinyl, piperidino and NHR'; Y and Z each independently selected from hydrogen and lower alkyl; and R is selected from the group consisting of hydrogen, formyl, acetyl, benzoyl, nitrobenzoyl and chlorinated benzoyl; and R' is selected from the group consisting of hydrogen, lower alkyl and lower alkenyl, cyclohexyl, phenalkyl of up to 8 carbon atoms, phenyl, chlorinated phenyl and anisyl; and certain salts of these compounds, which salts are selected from the group consisting of the Group I and II metals having an atomic number of up to 30, hydrochloride, pyridine, ammonium, lower aliphatic hydrocarbon amine, lower alkanol amine and aniline.

The most preferred compounds are those with the following structure:



The lower alkylamine salts, in particular the isopropyl amine salts, are preferred.

These compounds are prepared according to the method described in U.S. 3,794,758 issued to Franz, Dec. 10, 1974.

A pharmaceutical composition for treatment of mammals, and in particular, warm blooded animals and humans, comprising a pharmaceutical carrier and an

effective amount anti-cancer compound selected from the group consisting of a mixture of (1) N-phosphonoglycine derivatives and (2) N-chlorophenyl-carbamates or N-chlorophenylthiocarbamates is also useful herein.

C. HIV DRUGS

HIV is treated with two general classes of drugs, reverse transcriptase inhibitors and protease inhibitors. AZT and 3TC are widely used to treat acute HIV. The herbicidal and fungicidal agents and their derivatives can be used in conjunction with AZTor 3TC for the treatment of acute HIV. They do not interfere with the activity of the AZT.

Other HIV and antiviral agents can be used in conjunction with the therapy provided by this invention. These would include reverse transcriptase inhibitors and protease inhibitors. The drugs can be used concurrently or given in sequence with the herbicidal or fungicidal agents and their derivatives.

D. CHEMOTHERAPEUTIC AGENTS

The fungicides and herbicides can be administered with chemotherapeutic agents. This can be in sequence, where the chemotherapeutic agent is used to debulk the tumor and then the treatment with the herbicide, fungicide, or their derivatives begins, or the two materials can be administered together.

The chemotherapeutic agents are generally grouped as DNA-interactive Agents, Antimetabolites, Tubulin-Interactive Agents, Hormonal agents and others such as Asparaginase or hydroxyurea. Each of the groups of chemotherapeutic agents can be further divided by type of activity or compound. The chemotherapeutic agents used in the sequential method in combination herbicidal or fungicidal agents primarily include members of the DNA-interactive Agents, Antimetabolites, Tubulin-Interactive Agents groups. For a detailed discussion of the chemotherapeutic agents and their method of administration, see Dorr, et al, *Cancer Chemotherapy Handbook*, 2d edition, pages 15-34, Appleton & Lange (Connecticut, 1994) herein incorporated by reference.

In order to reduce the mass of the tumor or stop the growth of the cancer cells, the chemotherapeutic agent must prevent the cells from replicating and also must interfere with the cell's ability to maintain itself. The agents which do this are primarily the DNA-interactive agentsuch as Cisplatin, and tubulin interactive agents.

DNA-Interactive Agents include the alkylating agents, e.g. Cisplatin, Cyclophosphamide, Altretamine; the DNA strand-breakage agents, such as Bleomycin; the intercalating topoisomerase II inhibitors, e.g., Dactinomycin and Doxorubicin); the nonintercalating topoisomerase II inhibitors such as, Etoposide and Teniposide; and the DNA minor groove binder Plicamycin.

The alkylating agents form covalent chemical adducts with cellular DNA, RNA, and protein molecules and with smaller amino acids, glutathione and similar chemicals. Generally, these alkylating agents react with a nucleophilic atom in a cellular constituent, such as an amino, carboxyl, phosphate, sulfhydryl group in nucleic acids, proteins, amino acids, or glutathione. The mechanism and the role of these alkylating agents in cancer therapy is not well understood. Typical alkylating agents include:

Nitrogen mustards, such as Chlorambucil, Cyclophosphamide, Isofamide, Mechlorethamine, Melphalan, Uracil mustard;

aziridines such as Thiotepa;

methanesulfonate esters such as Busulfan;

nitroso ureas, such as Carmustine, Lomustine, Streptozocin;

platinum complexes, such as Cisplatin, Carboplatin;

bioreductive alkylator, such as Mitomycin, and Procarbazine, Dacarbazine and Altretamine;

DNA strand breaking agents include Bleomycin;

DNA topoisomerase II inhibitors include the following:

Intercalators, such as Amsacrine, Dactinomycin, Daunorubicin, Doxorubicin, Idarubicin, and Mitoxantrone;

nonintercalators, such as Etoposide and Teniposide.

The DNA minor groove binder is Plicamycin.

The antimetabolites interfere with the production of nucleic acids by one or the other of two major mechanisms. Some of the drugs inhibit production of the deoxyribonucleoside triphosphates that are the immediate precursors for DNA synthesis, thus inhibiting DNA replication. Some of the compounds are sufficiently like purines or pyrimidines to be able to substitute for them in the anabolic nucleotide pathways. These analogs can then be substituted into the DNA and RNA instead of their normal counterparts. The antimetabolites useful herein include:

folate antagonists such as Methotrexate and trimetrexate

pyrimidine antagonists, such as Fluorouracil, Fluorodeoxyuridine, CB3717, Azacytidine, Cytarabine, and Floxuridine

purine antagonists include Mercaptopurine, 6-Thioguanine, Fludarabine, Pentostatin;

sugar modified analogs include Cyctrabine, Fludarabine;

ribonucleotide reductase inhibitors include hydroxyurea.

Tubulin Interactive agents act by binding to specific sites on tubulin, a protein that polymerizes to form cellular microtubules. Microtubules are critical cell

structure units. When the interactive agents bind on the protein, the cell can not form microtubules Tubulin Interactive agents include Vincristine and Vinblastine, both alkaloids and Paclitaxel.

Adrenal corticosteroids are derived from natural adrenal cortisol or hydrocortisone. They are used because of their anti inflammatory benefits as well as the ability of some to inhibit mitotic divisions and to halt DNA synthesis. These compounds include, Prednisone, Dexamethasone, Methylprednisolone, and Prednisolone.

Hydroxyurea appears to act primarily through inhibition of the enzyme ribonucleotide reductase.

Asparagenase is an enzyme which converts asparagine to nonfunctional aspartic acid and thus blocks protein synthesis in the tumor.

The hormonal agents and leutinizing hormones are not usually used to substantially reduce the tumor mass. However, they can be used in conjunction with the chemotherapeutic agents or the herbicidal or fungicidal agents or their derivatives.

Hormonal blocking agents are also useful in the treatment of cancers and tumors. They are used in hormonally susceptible tumors and are usually derived from natural sources. These include:

estrogens, conjugated estrogens and Ethinyl Estradiol and Diethylstilbesterol, Chlorotrianisene and Idenestrol;

progestins such as Hydroxyprogesterone caproate, Medroxyprogesterone, and Megestrol;

androgens such as testosterone, testosterone propionate; fluoxymesterone, methyltestosterone;

Leutinizing hormone releasing hormone agents or gonadotropin-releasing hormone antagonists are used primarily the treatment of prostate cancer. These include leuprolide acetate and goserelin acetate. They prevent the biosynthesis of steroids in the testes.

Antihormonal antigens include:

antiestrogenic agentsuch as Tamosifen,

antiandrogen agentsuch as Flutamide ; and

antiadrenal agentsuch as Mitotane and Aminoglutethimide.

E. POTENTIATORS

The "potentiators" can be any material which improves or increases the efficacy of the pharmaceutical composition and/or act on the immune system. One such potentiator is triprolidine and its cis-isomer which are used in combination with

the chemotherapeutic agents and the fungicide or herbicide. Triprolidine is described in US 5,114,951 (1992). Another potentiator is procodazole, 1H-Benzimidazole-2-propanoic acid; [ß-(2-benzimidazole) propionic acid; 2-(2-carboxyethyl)benzimidazole; propazol). Procodazole is a non-specific active immunoprotective agent against viral and bacterial infections and can be used with the compositions claimed herein.

The potentiators can improve the efficacy of the herbicidal or fungicidal compounds and can be used in a safe and effective amount. These combinations can be administered to the patient or animal by oral, rectal, topical or parenteral administration.

Antioxidant vitamins such as ascorbic acid, beta-carotene, vitamin A and vitamin E can be administered with the compositions of this invention.

F. DOSAGE

Any suitable dosage can be given in the method of the invention. The type of compounds and the carriers and the amount will vary widely depending on the species of the warm blooded animal or human, body weight, and the virus or cancer, or tumor being treated. The range and ratio of the fungicidal or herbicidal agents and their derivatives and/or the chemotherapeutic agent used will depend on the type of agent and the cancer being treated. Generally, for the herbicidal or fungicidal agents and their derivatives a dosage of 2 milligrams (mg) per kilogram (kg) of body weight and as high as 4000 mg per kg of body weight is suitable. Higher dosages, up to 6000 mg/kg can also be used. Preferably as little as 15 mg to as much as 3000 mg/kg of body weight is used for the herbicidal or fungicidal agents. For the chemotherapeutic agents, a lower dosage may be appropriate, i.e., from as little as about 0.01 mg/kg of body weight to as much as about 400 mg/kg body weight, although amounts up to 1500 mg/kg can be used. Generally, the dosage in man is lower than for small warm blooded mammals such as mice. A dosage unit may comprise a single compound or mixtures thereof with other compounds or other cancer inhibiting compounds.

Any suitable dosage can be given in the method of the invention for treating HIV. The types of compounds and the carriers and the amount will vary widely depending on the species and the warm blooded animal or human body weight. The range and ratio of the fungicidal or herbicidal agents and their derivatives and the HIV treating agent used will depend on the type of agent. Generally, for the herbicidal or fungicidal agents and their derivatives a dosage of as little as about 0.2 milligrams (mg) per kilogram (kg) of body weight to as much as about 4000 mg per kg of body weight is suitable. Higher dosages, up to 6000 mg/kg can also be used.

Preferably from 2 mg or preferably about 20 mg/kg to as high a level as about 3000 mg/kg of body weight is used for the herbicidal or fungicidal agents and their derivatives. Generally, the dosage in man is lower than for small warm blooded mammals such as mice. A dosage unit may comprise a single compound or mixtures thereof with other compounds or other HIV treating compound.

The dosage unit can also comprise diluents, extenders, carriers and the like. The unit may be in solid or gel form such as pills, tablets, capsules, liposomes and the like or in liquid form suitable for oral, rectal, topical, intravenous injection or parenteral administration or injection into or around the tumor.

G. DOSAGE DELIVERY FORMS

The herbicide or fungicide and their derivatives are typically mixed with a pharmaceutically acceptable carrier. This carrier can be a solid or liquid or a liposome and the type is generally chosen based on the type of administration being used. The active agent can be coadministered in the form of a tablet or capsule, liposome, or as an agglomerated powder or in a liquid form. Examples of suitable solid carriers include lactose, sucrose, gelatin and agar. Capsule or tablets can be easily formulated and can be made easy to swallow or chew; other solid forms include granules, and bulk powders. Tablets may contain suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents. Oral dosage forms optionally contain flavorants and coloring agents. Parenteral and intravenous forms would also include minerals and other materials to make them compatible with the type of injection or delivery system chosen.

Specific examples of pharmaceutical acceptable carriers and excipients that may be used to formulate oral dosage forms of the present invention are described in US. Pat. No. 3,903,297 to Robert, issued Sept. 2, 1975. Techniques and compositions for making dosage forms useful in the present invention are described in the following references: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976).

H. METHOD OF TREATMENT

The method of treatment can be any suitable method which is effective in the treatment of the particular virus, cancer or tumor type that is being treated. Treatment may be oral, rectal, topical, parenteral or intravenous administration or by injection into the tumor and the like. The method of applying or administering an effective amount also varies depending on the tumor or virus being treated. It is believed that parenteral treatment by intravenous, subcutaneous, or intramuscular application of the herbicidal or fungicidal compounds, formulated with an appropriate carrier. Additional anti-viral materials can be used along with the herbicide or fungicide as well as additional cancer inhibiting compound(s) can be combined in the treatment. Diluents can be used to facilitate application or administration is the preferred method of administering the compounds to warm blooded animals.

For the treatment of viral infections, the herbicidal or fungicidal agent is administered in doses for 7 to about 21 days or longer if needed to inhibit the growth or to kill the virus. In the case of chronic infections, these agents may need to be given for extended periods of time, up to years.

For the treatment of acute viral infections or HIV, the herbicidal or fungicidal agent can be administered after an AZT treatment or in conjunction with other HIV therapies. These drugs can be also administered in a sequential regimen in which the HIV virus is first reduced in the body and then the herbicidal or fungicidal agent is administered to keep the virus from continuing to replicate. AZT therapy can be continued during the treatment with the herbicidal or fungicidal treatment. If the disease is in the early stages, the herbicidal or fungicidal agent can be administered to keep the virus from replicating or growing and thus slow the progress of the disease.

Preferably, in cancer treatments the herbicidal or fungicidal agent is administered first to significantly reduce the size of the cancer or tumor mass. Usually this will take 3 to about 14 days. The reduction in the tumor or level of cancer cells will be to less than 50% of the original level. Radiation therapy may be used in conjunction with the herbicidal or fungicidal agent treatment.

Once the tumor has been reduced, the herbicidal or fungicidal is administered. Because of the relative safety of this material, it can be administered for from 14 days to 365 days as needed to maintain its effectiveness in reducing the regrowth of the cancer.

The following examples are illustrative and are not meant to be limiting to the invention.

Benomyl is methyl 1-(butylcarbamoyl)-2-benzimidazolecarbamate.

Carbendazim is methyl 2-benzimidazole carbamate.

Thiabendazole is 2-(4-thiazolyl)-1H-benzimidazole.

Example 1

HIV Testing

HIV Virus Replication Study

Chlorpropham and thiabendazole were tested in chronically infected HIV virus. These cell populations contain integrated copies of the HIV genome and constitutively produce HIV at relatively high levels (CEM-SK1, U937-SK1 and H9-SK1 from Frederick Research Center, Maryland) or are latently infected and only produce virus after stimulation with phorbol esters, tumor necrosis factor or IL6 (U1 and ACH2). Virus products was reduced in all cell lines tested and the compounds did not stimulate virus production form the latently infected cells. Reductions in virus production were observed when quantifying supernatant reverse transcriptase activity, supernatant p24 as well as intracellular p24, indicating the compounds inhibit virus production at a step of replication prior to production of intracellular proteins.

Quantification of the infectivity of virions produced from the infected cells demonstrates reductions in the number of infectious virions in parallel with reductions in supernatant RT or p24, indicating that the compounds reduce the amount of virus produced, but not the quality of the virions. Inhibition of virus production from the chronically infected cells was observed at concentrations which were nontoxic to the target class. Thiabendazole inhibited virus production at concentrations great than 1-10μg/ml while chloropropham inhibited virus production at concentrations greater than 0.25μg/ml.

Toxicity to the chronically infected cells was similar to that observed with the uninfected cells. Evaluation of chloropropham and thiabendazole on chronically infected cells was performed by evaluation of thymidine (DNA), uridine (RNA) and leucine (protein) incorporation into cellular macromolecules. Inhibition of cellular macromolecule synthesis paralleled the toxicity of the two compounds as would be expected and did not occur at lower nontoxic concentrations found to inhibit virus production from the chronically infected cells.

After 28 days of treatment with these compounds on chronically infected cells, the toxicity of the compounds to the target cells appeared similar in both uninfected and chronically infected cells. The compounds do not preferentially kill HIV-infected cells. Reductions in the level of virus production were stable and were observed at concentration greater than 10 μg/ml for thiabendazole and greater than 1 μg/ml for chloropropham.

These results suggest that chloropropham and thiabendazole can quickly reduce the level of virus production from cell populations chronically infected with

HIV-1 and the antiviral effect is maintained with prolonged compound exposure. This reduction of virus production occurs at concentrations which are nontoxic to the host cell and which have no effect on the synthesis of cellular DNA, RNA and protein.

Virus Resistance Studies

Chronically infected HIV cells were cultured in the presence of thiabendazole at 1 μg/ml for the first month, 5 μg/ml for the second month, 10 μg/ml for the third month, 20 and 40 μg/ml for the fourth month and 80 μg/ml for the fifth and sixth months. Chloropropham was used at 1, 2, 4, 8 and 16 μg/ml for each of the six months. At the end of each month, the cells were evaluated for virus production compared to chronically infected cells not treated with the compounds. For each of the six months of treatment experience, no change in the antiviral effect of the compounds was noticed and the toxicity of the compounds remains identical. The compounds remain active against HIV and that resistance was not rapidly achieved via the selection of resistant viruses or adaptation of the cells to prevent compound induced toxicity. Virus production remains totally suppressed from cultures treated with thiabendazole at 40 and 80 μg/ml and chloropropham at 8 and 16 μg/ml.

Reappearance of Virus Production from Chronically Infected Cells Previously Treated

Chronically infected cells which were treated with compound for prolonged periods were washed free of compound and cultured to determine if, and when, virus production would resume. Cultures in which treatment resulted in the total elimination of virus production were used in these assays. These cultures included chronically infected cells cultured in the presence of 20, 40, and 80 μg/ml of thiabendazole and 4, 8, 16 μg/ml of chloropropham. Within 4 days virus production resumed from the cells cultured in the presence of the lower concentrations of each compound (20 μg/ml and 4 μg/ml). Virus production resumed at the 40 μg/ml concentration of thiabendazole by day 12 and at the 8 μg/ml of chloropropham by day 54. At the highest concentrations virus production was observed at approximately day 70.

Infectability of Cells Treated with Chloropropham and Thiabendazole

Cells which were pretreated with chloropropham and thiabendazole for a long period of time were washed free of compound and used as a target cell population. The cells were split into 3 populations and labeled Group 1, 2 or 3. Group 1 was treated with the compound for 24 hours (at the same concentration

used in the prolonged treatment phase), washed free of compound and cultured in the presence of infectious virus and fresh compound. Group 2 was pretreated for 24 hours, washed free of compound and cultured in the presence of infectious virus only. Group 3 was cultured for both the pretreatment and the infection phases in fresh medium only (no virus or compound). Virus production from the cell populations was identical irrespective of the culture conditions. These results indicate that the chronically infected cells treated for prolonged periods were not super-infected with HIV.

Additional Chronic HIV studies

Chronic HIV-1 infected cells U1 were derived from an acute HIV-1 infection of the promonocytic cell line, U937. The chronic HIV-1 infected cells, ACH-2 were derived from an acute HIV-1 infection of the T cell line, A3.01.

These cells were cultured in medium and the phorbol ester, PMA. PMA causes the cells (both U1 and ACH-2) to be activated and not divide but it also causes the U-1 cells to differentiate. This results in fewer cells in the PMA-treated cultures than the media alone cultures. Cell viability was measured when these cell lines were treated with the test compounds.

Both cell lines constituitively produce a small amount of HIV-1. ACH-2 cell lines tend to produce more HIV-1 than U1 cells as shown by p-24 ELISA. When either cell line is cultured in the presence of PMA there is an increase in the quantity of HIV-1 produced as measured by the p-24 antigen ELISA.

In addition, the number of institute positive HIV mRNA expressing cells per microscopic field is measured. Comparisons can be made from these numbers since the same number of cells were adhered to the glass slides for each drug concentration (10×10^6cells/ml).

These cells were treated with test samples. Thiabendazole at 60 µg/ml suppressed replication in the HIV monocytes by 74% and the T-cell HIV replication was increased by 26%. The positive control was AZT which suppressed HIV monocytes replication by 98% at 1 µg/ml and suppressed T-cell HIV replication by 60%. The therapeutic index (TI), the ratio of the toxic dose of drug to efficacious dose of drug for thiabendazole is 2.8 versus 12, 500 for AZT.

Acute HIV Model

In an acute HIV in vitro model, griseofulvin inhibited viral replication by 98% at 10µg/ml with a therapeutic index of 5.3. AZT, a known HIV drug, also inhibited viral replication by 98% at 1µg/ml with a therapeutic index of 12,500. The therapeutic index is the ratio of toxic dose of drug to efficacious dose of drug.

Example 2

Colon, Breast and Lung Tumor Cells Test

The following cell culture tests were performed to test the toxicity of the herbicidal or fungicidal compounds on colon, breast and lung human tumor cells. The viability of the cells were tested by looking at MTT (3-[4,5-dimethylthiazol-2-yl] -2,5-diphenyltetrazolium bromide) reduction. MTT assay is a well known measure of cell viability.

The colon tumor cells (HT29 from American Type Culture Collection (ATCC)) and the breast cells (MX1 from cell lines from ATCC) were cultured in Eagle's Miminal Essential Medium with 10% fetal bovine serum. The lung tumor cells (A549 from ATCC cell lines) were cultured in Ham's F12 medium with 10% fetal bovine serum.

The tumor cells were passaged and seeded into culture flasks at the desired cell densities. The culture medium was decanted and the cell sheets were washed twice with phosphate buffered saline (PBS). The cells were trypsinized and triturated prior to seeding the flasks. Unless otherwise indicated the cultures were incubated at 37 $\pm$ 1° C in a humidified atmosphere of 5$\pm$ 1% carbon dioxide in air. The cultures were incubated until they were 50-80% confluent.

The cells were subcultured when the flasks were subconfluent. The medium was aspirated from the flasks and the cell sheets rinsed twice with PBS. Next, the Trypsin Solution was added to each flask to cover the cell sheet. The Trypsin Solution was removed after 30-60 seconds and the flasks were incubated at room temperature for two to six minutes. When 90% of the cells became dislodged, growth medium was added. The cells were removed by trituration and transferred to a sterile centrifuge tube. The concentration of cells in the suspension was determined, and an appropriate dilution was made to obtain a density of 5000 cells/ml. The cells were subcultured into the designated wells of the 96-well bioassay plates (200 microliter cell suspension per well). PBS was added to all the remaining wells to maintain humidity. The plates were then incubated overnight before test article treatment.

Each dose of test article was tested by treating quadruplicate wells of cultures with 100 microliter of each dilution. Those wells designated as solvent controls received an additional 100 microliter of methanol control; negative controls wells received an additional 100 microliters of treatment medium. PBS was added to the remaining wells not treated with test article or medium. The plates were then incubated for approximately 5 days.

At the end of the 5 day incubation, each dose group was examined microscopically to assess toxicity. A 0.5 mg/ml dilution of MTT was made in treatment medium, and the dilution was filtered through a 0.45 micrometer filter to remove undissolved crystals. The medium was decanted from the wells of the bioassay plates. Immediately thereafter, 2000 microliter of the filtered MTT solution was added to all test wells except for the two untreated blank test wells. The two blank wells received 200 microliters of treatment medium. The plates were returned to the incubator for about 3 hours. After incubation, the MTT containing medium was decanted. Excess medium was added to each well and the plates were shaken at room temperature for about 2 hours.

The absorbance at 550 nm (OD_{550}) of each well was measured with a Molecular Devices (Menlo Park, CA) VMax plate reader.

The mean OD_{550} of the solvent control wells and that of each test article dilution, and that of each of the blank wells and the positive control were calculated. The mean OD_{550} of the blank wells was subtracted from the mean of the solvent control wells, and test article wells, respectively to give the corresponding mean OD_{550}.

$$\% \text{ of Control} = \frac{\text{corrected mean } OD_{550} \text{ of Test Article Dilution}}{\text{corrected mean of } OD_{550} \text{ of Solvent Control}} \times 100$$

Dose response curves were prepared as semi-log plots with % of control on the ordinate (linear) and the test article concentration on the abscissa (logarithmic). The EC_{50} was interpolated from the plots for each test article.

For the test articles administered in methanol, separate responses were prepared to correct for the methanol data.

Adriamycin was used as a positive control. In all cases, it was more toxic than any of the test materials by one or two logs. Adriamycin is one of the more potent agents in current use and one with significant side effects. The peak plasma concentration of other, quite effective chemotherapeutic agents may be 10 to 50 times higher than that of Adriamycin.

The EC_{50} is the concentration at which one half of the cells are killed.

The following tables show the results of this test for various fungicides and herbicides. The effect of these same materials on normal healthy cells is also provided.

Table 1

Test Material	EC-50 Result (ppm)					
	HT29	HT29	MX1	MX1	A549	A549
Adriamycin	0.03	0.006	0.02	0.001	0.03	0.009
benomyl	0.742	0.747	1.42	2.42	0.980	1.02
carbendazim	0.621	0.662	0.829	0.856	0.856	0.836

In normal healthy cells, the following results are obtained.

Table 2

Test Material	EC-50					
	Broncheal Cells		Kerotinoyle Cells		Fibroblasts	
Benomyl	0.728	0.682	3.26	2.4	3.24	2.81
Carbendazin	0.320	0.506	0.752	0.822	1.52	1.42
Adriamycin	0.015	0.0020	0.0035	0.0093	0.065	0.10

In a related study using lung tumor cells (A-549) breast tumor cells (MCF-7) and colon tumor cells (HT-29). thiabendazole, a systemic fungicide, effectively killed these cells. Table 3 summarizes the results.

Table 3

Concentration (ppm)	Optical Density		
	A-549	MCF-7	HT-29
0-Control	0.600	0.245	0.398
173	0.007	0.007	0.005
35	0.411	0.025	0.011
17.3	0.851	0.258	0.204
3.46	1.12	0.466	0.713
0.87	1.32	0.507	0.852

Results of tests with chloropropham are given in Tables 4 and 5.

Table 4

Test Material	EC-50 Result (ppm or microgram/ml)					
	HT29	HT29	MX1	MX1	A549	A549
Adriamycin	0.003	0.006	0.02	0.001	0.03	0.009
chloropropham	13.3	11.4	91.8	108	12.6	92.5

In normal healthy cells, the following results are obtained.

Table 5

Test Material	EC-50					
	Broncheal Cells		Kerotinoyle Cells		Fibroblasts	
chloropropham	0.002	>15.2	3.9	13.0	>152	64.2
Adriamycin	0.015	0.0020	0.0035	0.0093	0.065	0.10

Results of testing with glyphosate are provided in Tables 6 and 7.

Table 6

Test Material	EC-50 Result (ppm)					
	HT29	HT29	MX1	MX1	A549	A549
Adriamycin	0.003	0.006	0.02	0.001	0.03	0.009
glyphosate	5.41	3.73	36.5	14.6	25.9	22.3

In normal healthy cells, the following results were obtained:

Table 7

Test Material	EC-50					
	Broncheal Cells		Kerotinoyle Cells		Fibroblasts	
glyphosate	1.59	3.54	3.09	3.21	86.1	35.8
Adriamycin	0.015	0.0020	0.0035	0.0093	0.065	0.10

A mixture of chloropropham and glyphosate was also tested. The results are presented in Tables 8 and 9.

Table 8

Test Material	EC-50 Result (ppm)					
	HT29	HT29	MX1	MX1	A549	A549
Adriamycin	0.003	0.006	0.02	0.001	0.03	0.009
chloropropham	13.3	11.4	91.8	108	12.6	92.5
glyphosate	5.41	3.73	36.5	14.6	25.9	22.3
1:1 mixture*	1.96	1.61	9.70	8.78	10.8	10.1

* a mixture of chloropropham and glyphosate®.

In normal healthy cells, the following results were obtained:

Table 9

Test Material	EC-50					
	Broncheal Cells		Kerotinoyle Cells		Fibroblasts	
chloropropham	0.002	>15.2	3.9	13.0	>152	64.2
glyphosate	1.59	3.54	3.09	3.21	86.1	35.8
1:1 mixture*	0.001	0.497	0.242	0.286	129	5.95
Adriamycin	0.015	0.0020	0.0035	0.0093	0.065	0.10

* a mixture of chloropropham and glyphosate®

Table 10 shows the results of a test using Propiconazole.

Table 10

Test Material	EC-50 Result (ppm)		
	HT29	MX1	A549
Adriamycin	0.00639	0.00078	0.00373
Propiconazole	0.0331	0.0284	0.113

Leukemia Study

Mice are randomly selected and divided into groups for treatment. Five groups are infected with leukemia. The diseased animals are dosed for five days, off two days and then dosed for another five days and then three days off, then dosed for five days and off for two days. This dosing on and off in an irregular pattern was not an ideal regimen, but the results do show a positive benefit for the Carbendazim ™. One group of mice was treated with Cytoxan™, 2-[bis(2-chloroethyl)-amino-1-oxo-2-aza-5-oxophosphoridin, a control was dosed with canola oil and three groups were treated with various levels of Carbendazim™, methyl -(butylcarbamoyl)-2-benzimidazole-carbamate. A control with no treatment was also used. The Carbendazim™ was dosed at three levels 4000 mg/kg, 2500 mg/kg and 1000 mg/kg. The Cytoxan™ was dosed at 125 mg/kg. After 8 days, the no treatment group had lost 1 mouse, by day 10, 8 mice were dead and at day 11 all ten mice were dead. The mice in the Cytoxan™ group survived more than 21 days. The higher dose Carbendazim™ group had one mouse die on day 14, two died on days 15,16 and 17

and one each died on days 20, 21, and 22. The mean number of days for this group is 17.3. The intermediate dosage group had 2 mice die on day 14, 4 on day 15, 1 on day 16, 2 on day 19 and 1 on day 21. The mean number of days for this group is 16.50. The lowest dosage group had 2 mice die on day 12, 13, 14, and 15; and 1 died on each of days 16 and 17. The mean number of days for this group is 14.1.

In an in vivo mouse model for leukemia, P388, Carbendazin increased the life span of the mice versus control by 129% at 1000 mg/kg; by 148% at 2000 mg/kg and by 189% at 4000 mg/kg.

Mouse Cancer Model

In a mouse model for breast, lung and colon cancer Carbendazim slowed tumor growth. MXI breast cancer tumors implanted subcutaneously under the mice skin were treated with 500 mg/kg of Carbendazim. Tumor growth was slowed by 42%. Carbendazim slowed tumor growth in lung A549 tumors implanted subcutaneously under the mice skin by 57% at the same dose. In a screening test of HT29 tumors implanted subcutaneously under the mice skin, tumor growth was slowed 54% at 2500 mg/kg dose of Carbendazim.

In a mouse model for breast cancer cytoxan is administered to the animal reduce the tumor mass significantly. Carbendazim is administered to the mice at 4000, 5000, and 6000 mg/kg of body weight in a separate leg. The tumor continued to decrease in size and its regrowth was limited even after 180 days with the carbendazim treatment. The growth was dose dependent. The cytoxan treated control had tumor regrowth after 100 days; and when stimulated with estrogen at day 115 had a rapid regrowth. Even with estrogen stimulation, the carbendazim treated animals had no significant change in tumor mass. After 130 days, carbendazim is administered to the mice (at 4000, 5000, and 6000 mg/kg of body weight) that had been treated with Cytoxan. The tumor continued to decrease in size and its regrowth was limited even after 180 days.

In an in vivo mouse study for leukemia (P388), griseofulvin showed an increase in the survival time relative to a nontreated control of 156% at 4000 mg/kg dose; 188% at 5000 mg/kg dose; and 218% at 6000 mg/kg dose.

Mouse Model for Melanoma

In an in vivo mouse model for melanoma, B16, Carbendazin increased the life span versus control by 131% at 1000 mg/kg; by 163% at 2000 mg/kg and by 187% at 4000 mg/kg.

When the Carbendazin is combined with Navelbine at 0.5 mg/kg to 2.0 mg/kg, the effective dose of the Carbendazin is lowered in an in vivo mouse model for melanoma.

Dose Carbendazin (mg/kg)	Dose Navelbine (mg/kg)	% increase in survival time vs. untreated mice
4000	0.5	255
4000	1.0	298
4000	2.0	268
2000	0.5	259
2000	1.0	265
2000	2.0	287
1000	0.5	207
1000	1.0	233
1000	2.0	245
--	0.5	190
--	1.0	245
--	2.0	265

In an in vivo mouse study for melanoma (B16), griseofulvin showed an increase in the survival time relative to a nontreated control of 165% at 4000 mg/kg dose; 179% at 5000 mg/kg dose; and 201% at 6000 mg/kg dose. Cytoxan at 300 mg/kg showed an increased survival rate of 192%.

Example 3

Anti-Viral Evaluation with Human Influenza Virus

Female CD (mice Charles River Breeding Laboratories, Portage, MI) 5 to 7 weeks old of age at the time of receipt are used. Mice are approximately 6 to 9 weeks old and weigh approximately 20 to 28 grams at the time test initiation. All mice used in the study do not vary in age by more than 10 days. The mice are housed 6 per cage with bedding. The mice are fed rodent diet 5002 (PMI, St. Louis Missouri) ad libitum. Fresh water is supplied to the mice ad libitum.

Human influenza virus, strain AT2/Taiwan/1/64 is used to challenge the mice. The organism is stored at approximately -70°C. Prior to infectious challenge a vial of frozen stock is thawed and diluted to the appropriate concentration in buffered saline solution. The mice are anesthetized with Halothane and the virus challenge dose is administered intra-nasally in volume of 50 microlitres.

Test materials are administered at the concentration and volume as provided below. On days 1 through 14, 10 mice per group receive the test articles by oral lavage. Saline control animals (10) receive a comparable volume of saline as compared to the test article-dosed mice. Test article dosing is accomplished at

approximately 24 hour intervals. On day 0 approximately 4 hours after the second dosing of test articles or saline, all mice are challenged intra-nasally with an infective dose of virus calculated to produce approximately 90% lethality. Animals are observed daily for 21 days after infectious challenge for mortality or moribundity.

TEST MATERIAL	DOSE (mg/kg)	PERCENT MORTALITY
Fluconazole	350	0
Fluconazole	700	30%
Saline	-	100%
Amantadine	75	0%

At 175 mg/kg dose of Propiconazole 40% of the mice survived compared to a saline control in which no mice survived. At 350 mg/kg dose of Propiconazole 57% of the mice survived.

Example 4

Anti-Viral Evaluation with Rhinovirus

In an in vitro screening for Rhinovirus, type A-1, cell line WI-38, propiconazole was effective at 32 μg/ml. The positive control was A-36683 of Abbot Company, (S,S)-1,2-bis(5-methoxy-2-benzimidazolyl)-1,2-ethanediol. A-36683 has a therapeutic index of 1000-3200. Propiconazole has a therapeutic index of 1-3. (See Schleicher et al, *Applied Microbiology*, 23, No. 1, 113-116 (1972).

In an in vitro screening for Rhinovirus, type A-1, cell line WI-38, griseofulvin was effective at 100 μg/ml. The positive control was A-36683 of Abbot Company, (S,S)-1,2-bis(5-methoxy-2-benzimidazolyl)-1,2-ethanediol. A-36683 has a therapeutic index of 1000-3200. Griseofulvin has a therapeutic index of 1-2. (See Schleicher et al, *Applied Microbiology*, 23, No. 1, 113-116 (1972).

Example 5

In Vitro Human Tumor Colony Forming Units Test

Solid tumors removed by patients are minced into 2 to 5 mm fragments and immediately placed in McCoy's Medium 5A plus 10% heat inactivated newborn calf serum plus 1% penicillin/streptomycin. Within 4 hours, these solid tumors are mechanically disassociated with scissors, forced through No. 100 stainless steel mesh, through 25 gauge needles, and then washed with McCoy's medium as described above. Ascitic, pleural, pericardial fluids and bone marrow are obtained by standard techniques. The fluid or marrow is placed in sterile containers containing 10 units of preservative free heparin per ml. of malignant fluid or marrow. After centrifugation at 150 x g for 10 minutes, the cells are harvested and

washed with McCoy's medium plus 10% heat inactivated calf serum. The viability of cell suspensions is determined on a hemocytometer with trypan blue.

Cells to be cloned are suspended in 0.3% agar in enriched CMRL1066 supplemented with 15% heat inactivated horse serum, penicillin (100 units/ml), streptomycin (2mg/ml), glutamine (2mM), insulin (3 units/ml), asparagine (0.6 mg/ml), and HEPES buffer (2mM). For the continuous exposure test each compound is added to the above mixture. Cells are placed in 35 mm petri dishes in a top layer of agar over an underlayer of agar to prevent growth of fibroblasts. Three plates are prepared for each data point. The plates are placed in a 37°C incubator, and are removed on day 14 for counting of the number of colonies in each plate. The number of colonies (defined as 50 cells) formed in the 3 compound treated plates is compared to the number of colonies formed in the 3 control plates, and the percent colonies surviving at the concentration of compound can be estimated. Three positive control plates are used to determine survival rate. Orthosodium vanadate at 200 µg/ml is used as the positive control. If there is <30% colonies in the positive control when compared to the untreated control, the test is evaluated.

At concentration of 0.5 and 5.0 µg/ml in a single dose experiment propiconazole was not effective (0/1) against tumors in this test. At concentration of 50.0 µg/ml in a continuous exposure experiment propiconazole was effective against colon, lung (non-small cell) melanoma and ovarian cancers . Over all 6 of 8 had ≤ 50% survival.

At concentration of 0.5 and 5.0 µg/ml in a single dose experiment griseofulvin was not effective (0/1) against tumors in this test. At concentration of 50.0 µg/ml in a continuous exposure experiment griseofulvin was effective against colon, lung, non-small cell, and ovarian cancers . Over all 5 of 6 had ≤50% survival.

At concentrations of 0.5 and 5.0 µg/ml in a continuous exposure experiment or single dose experiment Fluconazole was not effective (0/3 and 0/13 respectively) against tumors. At concentration of 50.0 µg/ml in a continuous exposure experiment Fluconazole was effective against lung, non-small cell, and ovarian cancers particularly. Over all 4 of 13 had ≤50% survival.

What is claimed is:

1. A pharmaceutical composition for treating viral infections in warm blooded mammals comprising 700 mg to 6000 mg of a member selected from the group consisting of herbicides, fungicides, herbicide derivatives, fungicide derivatives, the pharmaceutically acceptable organic or inorganic acid addition salts thereof, and mixtures thereof with a pharmaceutically acceptable carrier.

2. A pharmaceutical composition according to Claim 1 wherein said viral infection caused by a virus containing genetic material from plants, fungi or molds.

3. A pharmaceutical composition according to Claim 1 or 2 wherein said viral infection is an HIV infection.

4. A pharmaceutical composition according to Claim 3 wherein an antiviral agent, preferably a transcriptase inhibitor or a protease inhibitor is added to the pharmaceutical composition.

5. A pharmaceutical composition according to Claim 1, 2, 3 or 4 having from about 3000 mg to about 6000 mg of said herbicide or fungicide is in the composition.

6. A pharmaceutical composition according to Claim 5 prepared in a liquid form selected from the group consisting of aqueous solutions, alcohol solutions, emulsions, suspensions, and suspensions reconstituted from non-effervescent and effervescent preparations and suspensions in pharmaceutically acceptable fats or oils.

7. A pharmaceutical composition according to Claim 3, 4 or 5 wherein an HIV drug is added to said pharmaceutical composition..

8. A pharmaceutical composition according to Claim 1, 2 ,3,4, 5,6 or 7 wherein a potentiator is added to said pharmaceutical composition.

9. A pharmaceutical composition for treating cancer comprising from 700 mg to 6000 mg of a member selected from the group consisting of a herbicide, a fungicide, a herbicide derivative, a fungicide derivative or the pharmaceutically acceptable organic or inorganic acid addition salts thereof to a pharmaceutically acceptable carrier.

10. A pharmaceutical composition according to Claim 9 wherein said cancer cells contain genetic material from plants, fungi or molds.

11. A pharmaceutical composition according to Claim 9 or 10 wherein a potentiator is added to said pharmaceutical composition.

12. A pharmaceutical composition according to Claim 10 or 11 comprising from about 3000 mg to about 6000 mg of said herbicide or fungicide or fungicide derivative or herbicide derivative.

13. A pharmaceutical composition according to Claim 12 wherein a chemotherapeutic agent is added with said herbicide or fungicide.

14. A pharmaceutical composition according to Claim 13 wherein said chemotherapeutic agent is selected from the group consisting of DNA-interactive Agents, Antimetabolites or Tubulin-Interactive Agents, preferably, Asparaginase, hydroxyurea, Cisplatin, Cyclophosphamide, Altretamine; Bleomycin, Dactinomycin, Doxorubicin, Etoposide, Teniposide, and Plicamycin, Methotrexate, Fluorouracil, Fluorodeoxyuridine, CB3717, Azacytidine, Cytarabine, Floxuridine, Mercaptopurine, 6-Thioguanine, Pentostatin, Cyctrabine, and Fludarabine.

15. A pharmaceutical composition according to Claim 14 wherein said chemotherapeutic agent is in the form of a liposome.

16. A pharmaceutical composition according to Claim 9, 10, 11, 12, 13, 14, or 15 wherein from about 0.5 mg to about 400 mg of chemotherapeutic agent is used.

17. A pharmaceutical composition according to Claim 13, 14, 15 or 16 wherein said herbicide or fungicide is a liquid form selected from the group consisting of aqueous solutions, alcohol solutions, emulsions, suspensions, and suspensions reconstituted from non-effervescent and effervescent preparations and suspensions in pharmaceutically acceptable fats or oils.

(18) A method for making a pharmaceutical composition for treating viral infections in warm blooded mammals comprising mixing a safe and effective amount of a member selected from the group consisting of herbicides, fungicides, herbicide derivatives, fungicide derivatives, the pharmaceutically acceptable organic or inorganic acid addition salts thereof, and mixtures thereof with a pharmaceutically acceptable carrier.

19. A method according to Claim 1 wherein said pharmaceutical compositions is prepared to treat viral infection caused by a virus containing genetic material from plants, fungi or molds.

20. A method according to Claim 1 or 2 wherein said viral infection is an HIV infection.

21. A method according to Claim 3 wherein an antiviral agent, preferably a transcriptase inhibitor or a protease inhibitor is added to the pharmaceutical composition.

22. A method according to Claim 1, 2, 3 or 4 wherein from about 0.2 mg to about 6000 mg of said herbicide or fungicide is used in making the composition.

23. A method according to Claim 5 wherein the mixture is prepared in a liquid form selected from the group consisting of aqueous solutions, alcohol solutions, emulsions, suspensions, and suspensions reconstituted from non-effervescent and effervescent preparations and suspensions in pharmaceutically acceptable fats or oils.

24. A method according to Claim 3, 4 or 5 wherein an HIV drug is added to said herbicide or fungicide pharmaceutical composition..

25. A method according to Claim 1, 2 ,3,4, 5,6 or 7 wherein a potentiator is added to said pharmaceutical composition.

26. A method for making a pharmaceutical composition for treating cancer comprising adding a safe and effective amount of a herbicide, a fungicide, a herbicide derivative, a fungicide derivative or the pharmaceutically acceptable organic or inorganic acid addition salts thereof to a pharmaceutically acceptable carrier.

27. A method according to Claim 9 wherein said composition is prepared to treat a cancer containing genetic material from plants, fungi or molds.

28. A method according to Claim 9 or 10 wherein a potentiator is added to said pharmaceutical composition.

29. A method according to Claim 11 wherein from about 2 mg to about 4000 mg of said herbicide or fungicide or fungicide derivative or herbicide derivative is added.

30. A method according to Claim 12 wherein a chemotherapeutic agent is added with said herbicide or fungicide.

31. A method according to Claim 13 wherein said chemotherapeutic agent is selected from the group consisting of DNA-interactive Agents, Antimetabolites or Tubulin-Interactive Agents, preferably, Asparaginase, hydroxyurea, Cisplatin, Cyclophosphamide, Altretamine; Bleomycin, Dactinomycin, Doxorubicin, Etoposide, Teniposide, and Plicamycin, Methotrexate, Fluorouracil, Fluorodeoxyuridine, CB3717, Azacytidine, Cytarabine, Floxuridine, Mercaptopurine, 6-Thioguanine, Pentostatin, Cyctrabine, and Fludarabine.

32. A method according to Claim 14 wherein said chemotherapeutic agent is prepared in the form of a liposome.

33. A method according to Claim 9. 10, 11, 12, 13, 14, or 15 wherein from about 150 mg to about 4000 mg of said herbicide or fungicide is added and from about 0.5 mg to about 400 mg of chemotherapeutic agent is used.

34. A method according to Claim 13, 14, 15 or 16 wherein said herbicide or fungicide is prepared in a liquid form selected from the group consisting of aqueous solutions, alcohol solutions, emulsions, suspensions, and suspensions reconstituted from non-effervescent and effervescent preparations and suspensions in pharmaceutically acceptable fats or oils.

INTERNATIONAL SEARCH REPORT

Intern: al Application No
PCT/US 97/21564

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/41 A61K31/415 A61K31/66

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 32115 A (PROCTER & GAMBLE) 17 October 1996 see the whole document ---	1,5,6,8, 9,11-14, 16-18, 22,23, 25,26, 28-30
X	WO 96 32103 A (PROCTER & GAMBLE) 17 October 1996 see the whole document --- -/--	1,3,5,6, 9,16-18, 26,29,34

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
10 March 1998	26. 03. 98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Klaver, T

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interr al Application No
PCT/US 97/21564

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 32104 A (PROCTER & GAMBLE) 17 October 1996 see the whole document ---	1,5,6,8, 9,11-14, 16-18, 22,23, 25,26, 28-30
X	WO 97 05873 A (PROCTER & GAMBLE) 20 February 1997 see the whole document ---	1,5,6,8, 9,11-14, 16-18, 22,23, 26,28-30
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1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int tional application No.
PCT/US 97/21564

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claims Nos.: 1,9,18,26
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

It is not clear exactly which compounds are defined by descriptors like 'herbicides','herbicide derivatives', 'fungicides', etc. The search has been limited to the general concept of the invention and the compounds mentioned in the claims and/or description.

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ial Application No
PCT/US 97/21564

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